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<b>(21) International Application Number:</b> PCT/US96/16417 <b>(22) International Filing Date:</b> 11 October 1996 (11.10.96)  <b>(30) Priority Data:</b> 60/005,194      13 October 1995 (13.10.95)      US  <b>(71) Applicant (for all designated States except US):</b> THE PENN STATE RESEARCH FOUNDATION [US/US]; 207 Old Main, University Park, PA 16802 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SELVARAJ, Ulagaraj [IN/US]; 1904 Loganwood Drive, Apex, NC 27502 (US). MESSING, Gary, L. [US/US]; 814 W. Foster Avenue, State College, PA 16801 (US).  <b>(74) Agent:</b> MONAHAN, Thomas, J.; The Pennsylvania State University, Intellectual Property Office, 113 Technology Center, University Park, PA 16802 (US).		<b>(81) Designated States:</b> JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> SYNTHESIS OF DRUG NANOPARTICLES BY SPRAY DRYING  <b>(57) Abstract</b>  The present invention relates to a method for synthesizing nanoparticles comprising combining an agent and a matrix to form a composite mixture, and spray drying the composite mixture, wherein the nanoparticles are less than about 5000 nm. Suitable agents that can be formulated into nanoparticle in the context of the present invention include therapeutic and diagnostic agents, cosmetic, dye, photographic, food, pesticide agents, among others.		

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## SYNTHESIS OF DRUG NANOPARTICLES BY SPRAY DRYING

The present invention relates to the field of drug manufacture, and, in particular, to the synthesis of therapeutic, diagnostic, analgesic, and antiinflammatory compositions having a median particle size less than about 5000 nm.

5        When a drug is administered into a body, it typically must cross a series of membranes before reaching the site of action where its activity can have a desired effect. For example, oral administration of a drug having a systemic site or sites of action will provide limited or no relief unless the drug crosses the gut wall. The ability  
10       of a drug to cross the gut wall can be controlled by the way in which the active substance is formulated. The formulation can also provide control as to the site of action of a given drug, and the rate at which the drug is available at that site. For instance, the same amount of  
15       drug could have a different effect when administered as an oral solution than when administered as a tablet because of the differences in the rate at which the drug is absorbed from the gut in the two cases.

One approach to the delivery of an orally administered drug that must cross the gut wall to be effective uses nanoparticles of the  
20       drug. Experimental results have shown that latex particles of diameter 200 nm can cross through the gastrointestinal (GI) tract across gut-associated lymphoid tissue known as Payers patches. Thomson et al., *Nature*, 188, 586 (1960). Recently, Jani et al., *J. Pharm. Pharmacol.*, 42, 821 (1990), demonstrated the transport of

50 to 3000 nm polystyrene latex particles across the Payers patches, with the smaller particles exhibiting the greatest uptake. Further benefits of the use of nanoparticles include the fact that drugs administered as nanoparticles have increased surface areas  
5 relative to larger sized drug particles, which correlates with increased absorption and utilization of the drug. Prescott et al., *Clin. Pharm. Therap.*, 11, 496.

As an example of the need for organic nanoparticles, consider naproxen, the dextrorotatory isomer of  
10 6-methoxy- $\alpha$ -methyl-2-naphthalene acetic acid. Naproxen has been shown to possess analgesic and anti-inflammatory activity in the treatment of rheumatoid arthritis, for example, for which naproxen nanoparticles can be more effective than aspirin, indomethacin, ibuprofen, and fenoprofen. These nanoparticles are better tolerated,  
15 thus enabling more patients to continue with the treatment. When naproxen nanoparticles of less than 400 nm are administered orally in humans, enhanced analgesic and anti-inflammatory activity can be achieved at a rapid rate. However, a less pronounced analgesic and anti-inflammatory activity is observed only after 5 to 6 hours of oral  
20 administration of larger naproxen particles, such as those larger than 20  $\mu$ m.

Another specific use of nanoparticles is as agents for X-ray diagnostic medical imaging. For example, organic nanoparticles, such as iodine-substituted ethyl benzoates, iothalamates, metrizoates  
25 and iodipamides, have been identified for X-ray contrast imaging because of their low solubility in aqueous media (less than about 10 mg/mL), and not being radioactive. Such nanoparticles provide effective imaging of tissue or fluid sites of the human body for up to

2 h and longer when administered intravenously as aqueous colloidal dispersions for the imaging of blood pool, liver, kidney, bone marrow, lymph nodes and spleen, for example. See EP 0 498 482 A2 and US Patents 5,145,684; 5,298,262; 5,233,995; and 5,302,401.

Current methods of producing nanoparticles result in a lack of uniformity of size or include contamination of the resultant nanoparticles by the process of production. For example, drawbacks of current methods can be visualized with respect to the process by which naproxen nanoparticles are currently prepared, i.e., by wet grinding of larger naproxen crystals using grinding media such as yttria stabilized zirconia, zirconium silicate and glass. The drawbacks of the method include a broad-size distribution of resultant particles, inherent contamination from the grinding media, and several hours of grinding necessary to achieve particles of the required average size; however, this method usually produces particles that include those of a size larger than 1  $\mu\text{m}$  as well. See, for example, US patent 4,540,642. Other current approaches to the generation of nanoparticles include that of US Patent 4,107,288. None display the requisite versatility with respect to ranges of drugs usefully administered via nanoparticles or provide nanoparticles of a sufficiently narrow range of size per manufacturing operation.

Accordingly, there is an unmet need in the pharmaceutical industry to synthesize organic drug nanoparticles, particularly those of a median size that is less than about 5000 nm, and more preferably of a median size that is less than about 400 nm.

### SUMMARY OF THE INVENTION

A novel spray drying method has been developed to synthesize drug nanoparticles having median sizes of less than about 5000 nm. This method involves spray drying different concentrations of the drug dissolved in dimethyl sulfoxide (DMSO),  
5 1-methyl-2-pyrrolidinone (12 MPO), ethanol, or water, with or without surfactants, sugars including sucrose, D(+) -lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbitol, D(+) -glucose and D-mannitol, and stabilizers. More specifically, this invention relates  
10 to how the precursor chemistry can be manipulated that leads to the formation of drug particles as small as less than about 40 nm, and the versatility of the method in mass producing nanocomposite powders, which can be rehydrated in the presence of suitable surfactants including a polaxamer, such as Pluronic™ F-68, a  
15 polyoxyethylene alcohol, such as Brij® 30, a nonoxynol, such as Igepal CO-520®, and Tetronic™ 908, and polymeric stabilizers including polyvinyl alcohol-polyvinyl acetate copolymers to form pharmaceutically acceptable drug nanoparticle formulations. These  
nanoparticle drug formulations can be delivered to various sites in  
20 the body as capsules, tablets, and colloidal suspensions.

In particular, the present invention is directed to a method for synthesizing nanoparticles comprising (a) combining an agent and a matrix material to form a composite mixture; and (b) spray drying the composite mixture, forming a nanocomposite. Preferably, the matrix  
25 material is at least 10% of the nanocomposite. The agent can be a diagnostic, therapeutic, cosmetic, dye, photographic, food, pesticide agent, or metal catalyst. Preferably, the diagnostic agent is any suitable agent used to diagnose a disease or condition, such as, but

not limited to, ethyl 3,5-diacetamido-2,4,6-triiodobenzoate.

Preferably, the therapeutic agent is any suitable agent for the treatment of a disease or condition selected from the group

consisting of, but not limited to, an antiinflammatory agent, an

5 antibiotic agent, an antifungal agent, an antiviral agent, an

antineoplastic agent, an immunosuppressive agent, an

immunostimulatory agent, an odor masking agent, an insect repelling

agent, an anesthetic agent, an antiseptic agent, an antioxidant, an

antihistamine, an antidiabetic agent, an antiepileptic agent, a muscle

10 relaxant, a stimulant, an antiallergic agent, a liposaccharide

complexing agent, a vitamin, a hormone, an anticancer agent, and a

cough suppressant. A preferred antiinflammatory agent is naproxen.

The nanoparticles of the present invention are formulated as a

colloidal suspension, capsule, tablet, or powder. The ratio of agent

15 to matrix material used in the context of the present invention is

from about 10:1 to about less than 1:100, as judged from analysis

of the nanocomposite; and the agent and matrix material are

combined in the presence of organic and aqueous solvents. The

present method further comprises atomizing the composite mixture,

20 which preferably forms droplets of from about 1  $\mu\text{m}$  to about 100

$\mu\text{m}$ , more preferably from about 1  $\mu\text{m}$  to about 75  $\mu\text{m}$ , and yet more

preferably from about 1  $\mu\text{m}$  to about 50  $\mu\text{m}$ .

The nanoparticles produced in the context of the present

invention have a median size that is less than about 5000 nm.

25 Preferably, the nanoparticles have a median size of less than about

1000 nm. More preferably, the nanoparticles have a median size of

less than about 400 nm. Most preferably, the nanoparticles have a

median size of less than about 250 nm.

The nanoparticles of the present invention are produced amidst a matrix, wherein the matrix is formed from a matrix material comprising a carbohydrate, a protein, an inorganic salt, a resin, or a lipid. Preferably, the carbohydrate is a sugar selected from the group consisting of sucrose, glucose, fructose, mannose, maltose, 5 D(+) -lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbitol, and D-mannitol. The carbohydrate can also be selected from the group consisting of cellulose acetate, cellulose acetate phthalate, carboxymethyl cellulose, ethyl cellulose, carboxymethyl cellulose calcium or sodium, methylcellulose, hydroxycellulose, hydroxy 10 propylcellulose, hydroxy propylmethylcellulose phthalate, noncrystalline cellulose, starch, and arabinogalactose. In other embodiments, the carbohydrate is a natural polysaccharide selected from the group consisting of gum arabic (acacia), gum ghatti, karaya, 15 tragacanth, locust bean, guar and xanthan gum. In yet other embodiments, the inorganic salt is selected from the group consisting of sodium chloride, potassium chloride, sodium bisulfite, sodium metabisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, sodium benzoate, calcium stearate, calcium carbonate, 20 barium sulfate, sodium salicylate, sulfathiazole sodium salt, alumina salts, magnesia salts, alumina-magnesia salts, formed from *inter alia* aluminum hydroxide, and the like. In another embodiment, the protein is collagen, gelatin, or zein. In yet other embodiments, the alumina salts, magnesia salts, alumina-magnesia salts, formed from 25 *inter alia* aluminum hydroxide, and the like, forms a gel. The resin is selected from the group consisting of polyvinylpyrrolidone, polyvinyl alcohol, polyarylic acid, polyethylene, polymethacrylate, polyamide (nylon), poly [ethylene-vinyl acetate], and shellac; the lipid is



selected from the group consisting of synthetic and natural phospholipids, glyceryl esters, paraffin, carnauba, spermaceti, beeswax, steric acid, stearyl alcohol and glycerol stearates; the protein is gelatin, zein, or collagen. Preferably the matrix further  
5 comprises a stabilizer, a surface modifier, a disintegrating agent, or a lubricating, which may include compounds listed above.

In a preferred embodiment of the present invention, the nanoparticle comprises ethyl 3,5-diacetamido-2,4,6-triiodobenzoate as the diagnostic agent and the nanoparticles have a median size of  
10 from about 160 nm to about 280 nm.

In another preferred embodiment of the present invention, the nanoparticle comprises an antiinflammatory agent such as aspirin, naproxen, indomethacin, ibuprofen, fenoprofen or acetaminophen or an antibiotic agent selected from the group of penicillins,  
15 tetracyclins, aminoglycoside antibiotics, and clindamycin.

A preferred embodiment of the present invention provides a method for synthesizing nanoparticles comprising naproxen as the antiinflammatory agent, sucrose as the matrix, polyvinyl alcohol-polyvinyl acetate copolymers, Pluronic™ F-68, or Tetronic™  
20 908, and the nanoparticles have a median particle size of from about 90 nm to about 185 nm.

Another preferred embodiment of the present invention is a pharmaceutical formulation comprising a nanoparticle synthesized by a method comprising (a) combining an agent and a matrix; and (b)  
25 spray drying the combined agent and matrix; and a pharmaceutical carrier.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of illustrative spray drying equipment used in the context of the present invention.

Fig. 2 is a diagram relating to the stages of the spray drying process.

Fig. 3 is a graph that depicts the results of an energy dispersive analysis by X-ray, demonstrating the presence of the iodine atoms of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1) throughout the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate-containing nanoparticles.

Fig. 4 is a graph depicting median particle size as a function of the initial concentration of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1).

Fig. 5 is a graph depicting median particle size as a function of the initial concentration of Pluronic™ F-68.

Fig. 6 is a graph depicting the change in particle size distribution of spray dried ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1) as a function of sonication time.

Fig. 7 is a graph depicting x-ray diffraction results of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1) nanoparticles comparing conventionally precipitated powders and spray-dried powders.

Fig. 8 is a graph depicting x-ray diffraction results of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1) nanoparticles generated in the presence or absence of Pluronic™ F-68.

Fig. 9 is a graph depicting x-ray diffraction results of ethyl cellulose powder and spray dried naproxen-ethyl cellulose nanocomposite.

## DESCRIPTION OF THE INVENTION

This invention is directed towards the synthesis of nanoparticles that are formed in the context of a matrix, and the combination of the nanoparticles in the matrix is herein referred to as a  
5 nanocomposite. A nanoparticle is formed substantially of an active agent ("the agent") and is between about 10 nm and about 5000 nm in size. A nanoparticle substantially formed of the agent is a nanoparticle that is at least about 80% by weight composed of the agent, more preferably at least about 90%, yet more preferably at  
10 least about 95%, and most preferably at least about 99%; the remainder of the content of a nanoparticle is composed of surface modifiers, surfactants, and other matrix material discussed hereinbelow. (Note that all percentages recited in this specification with respect to proportional content are proportions by weight,  
15 unless otherwise labeled).

The nanoparticles synthesized in the context of the present invention are preferably uniform in spatial distribution with respect to the matrix, as seen by electron microscopy. For example, for nanoparticles having a size between about 10 nm and about 100  
20 nm, such nanoparticles are found within about 200 nm to about 500 nm of each other; for nanoparticles having a size between about 200 nm and about 400 nm, such nanoparticles are found within about 400 nm to about 1000 nm of each other; and for nanoparticles having a size between about 1000 nm and about 5000 nm, such  
25 nanoparticles are found within about 2000 nm to about 3000 nm of each other. The nanoparticles synthesized in the context of the present invention preferably are uniform in distribution of size for a given set of process parameters used to generate the nanoparticles, which process parameters are further discussed hereinbelow. For

example, for a set of process parameters that can be determined by one of ordinary skill using the teaching of this application, at least more than about 10% of the nanoparticles can be synthesized having a given size, more preferably, at least more than about 50%  
5 of the nanoparticles can be synthesized having a given size, and yet more preferably, at least more than about 90% of the nanoparticles can be synthesized having a given size.

These nanoparticles are synthesized dispersed within a matrix within or by which the nanoparticles are formed. Any material  
10 included in a nanocomposite that is not a nanoparticle is considered herein to be part of the matrix, and the matrix can be a porous or a dense structure. A suitable matrix material is any chemical, compound, or structure that is a solid at room temperature (i.e., about 25°C), including but not limited to the examples set forth  
15 hereinbelow.

Within the context of the present invention, the size of a nanoparticle is less than about 5000 nm and at least about 10 nm, preferably less than about 1000 nm, more preferably less than about 400 nm, and most preferably less than about 250 nm. The material  
20 of the matrix ("the matrix material") is in a solid or solute phase, or the dried product thereof, and forms the aforementioned matrix. The combination of the agent and the matrix material is referred to herein as the "composite mixture," from which, upon spray drying, is formed the aforementioned nanocomposite. The composite mixture,  
25 particularly in the presence of a solvent, which, as further discussed below, can be organic or aqueous or both, forms a solution, which is preferred, or a suspension. If the composite mixture forms a suspension, the particulate matter within the mixture may require

further processing to allow formation of nanoparticles of the present invention. For example, if the agent is present as particles that are greater or similar to the size of nanoparticles desired, then the present process includes a step to reduce the size of the agent.

5 Similarly, the matrix material may require a size reduction to assure the desired size of nanocomposite, and of the resultant nanoparticles. Such further processing involves any suitable process for size reduction of such particulate matter, such as, but not limited to, sonication, microfluidization, or milling, or a combination thereof,  
10 using methods known to the art.

The composite mixture is preferably a solution, although in an alternative embodiment, the composite mixture is a suspension, wherein the suspended particulate matter can be agent or matrix material, and preferably is matrix material only. The composite  
15 mixture comprises a sufficient concentration of matrix material that, upon spray drying, a matrix is believed to be formed by the so-treated matrix material. The dissolved agent included in the composite mixture is believed to be contained within pores or upon the surface of the matrix, by which the agent forms nanoparticles in  
20 the spray drying process. Matrix material can constitute over 99% of the nanocomposite. Preferably, the matrix material comprises about 60% of the nanocomposite. In another embodiment, the matrix material comprises about a majority of the nanocomposite, more preferably the matrix material comprises about 40% of the  
25 nanocomposite, even more preferably the matrix material comprises about 25% of the nanocomposite, yet more preferably the matrix material comprises about 15% of the nanocomposite, and most

preferably, the matrix material comprises about 10% of the nanocomposite.

In the course of spray drying, which is further described below, solvent included with the composite mixture is removed by  
5 evaporation, thereby increasing the concentration and viscosity of the matrix material, which in turn restricts the mobility (via diffusion, for example) of the agent while in solution. Additionally, the matrix is believed to be formed by the matrix material in this process and is believed to confine the distribution of the agent included in the  
10 composite mixture within the surface structure of the matrix. Thus, the agent is believed to supersaturate and thereafter precipitate as a consequence of inherent properties of the matrix material, such as viscosity, molecular weight, porosity, pore size, and the like. Viscosity of the matrix can range from about 100 cp to about  
15 100,000 cp, preferably from about 100 to about 5,000 cp, and more preferably from about 100 cp to about 1,000 cp. Preferred matrices have a porous structure, which porosity is preferably from about 10% to about 90%, more preferably from about 50% to about 90%. Preferred pore size of the matrix material or resultant matrix is  
20 from about 5 nm to about 500 nm, more preferably from about 10 nm to about 100 nm.

The process by which the nanocomposite is formed is spray drying. Spray drying is a process of converting a liquid into a powder by spraying the liquid into a hot drying gaseous medium.  
25 This process constitutes: (i) generation of liquid aerosol droplets, (ii) evaporation of solvent from these droplets resulting in solution supersaturation, and (iii) nucleation and crystallization of the supersaturated solution within the droplets. See Fig. 2 for a diagram

of the process with respect to coprecipitation of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (referred to herein as "CMP-1"; manufactured by Nanosystems, Inc., Collegeville, PA) and sugar; and Masters, *Spray Drying Handbook*, 4th edition, Longman, Wiley & Sons (1985). Precipitation at low supersaturations can result in a single crystal, whereas high supersaturations yield nanosized precipitates. The particle morphology also depends on the drying conditions. In general, a particle formed by spray drying of solution is composed of many crystallites. Furthermore, the nature of the solvent and the addition of surfactant to the solution can affect the nucleation and growth processes, and hence the crystallite size. In order to synthesize a narrow distribution of nanoparticles by crystallization, an instantaneous nucleation has to be induced throughout the solution, and agglomeration must be avoided. Accordingly, preferably the residence time of the composite mixture in the spray dryer is no more than about 25 seconds, more preferably no more than about 15 seconds, and most preferably no more than about 10 seconds. Furthermore, as is known in the art, Ostwald ripening must be prevented.

Experimental parameters that can be varied to engineer particles of desired morphologies using methods well-known in the art. For example, hollow particles comprising single crystals or solid single crystals, hollow crust, crystal platelets, or needle-shaped crystal can be preferably produced by implementing suitable alterations to the spray drying process with respect to temperature, humidity, solvent evaporation rate, solute solubility, interfacial energy, particle mass and crystal growth rates. See Leong, *J. Aerosol Sci.*, **18** (5), 525 (1987) for a discussion of these standard methods. By varying the

evaporation and crystal growth rates and solubility, solid single crystal particles or particles consisting of an ensemble of small crystals can be obtained. The particle size and morphology can be varied by altering the initial concentration of the solution, surfactant concentration, and otherwise altering the composite mixture. Messing et al., *J. Am. Ceram. Soc.*, **76**, 2707 (1993). The attachment of surfactants onto the surface of the spray dried nanoparticle can facilitate subsequent nanoparticle stability and stability in liquid media. During spray drying, the as-produced spheres can rupture into several sphere fragments.

Spray drying has been employed in the pharmaceutical industry for: (i) drying a variety of heat sensitive biological materials, including plasma, proteins, enzymes, sera, microorganisms and yeasts; (ii) improving the solubility of water-soluble substances; (iii) increasing the flow properties of free-flowing granules for tablet preparation; and (iv) improving the dispersibility of methylcellulose. Broadhead et al., *Drug Development and Industrial Pharmacy*, **18** (11&12), 1169 (1992). However, prior uses of spray drying have not provided nanoparticles of uniform median sizes, such as those of less than about 5000 nm, more preferably of less than about 1000 nm, yet more preferably of less than about 400 nm, and most preferably of less than about 250 nm; and greater than at least about 10 nm.

Nanoparticles of the present invention are preferably prepared in the presence of matrix material that forms a solid at room temperature (about 25°C), such as a carbohydrate, including a sugar selected from the group consisting of sucrose, D(+)-lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbose, glucose, fructose, mannose,



maltose, sorbitol, and D-mannitol. Other carbohydrates, discussed further below, can also be used as the matrix of the nanocomposite. Nanoparticles are also preferably prepared in the presence of stabilizers such as polyvinyl alcohol-polyvinyl acetate copolymers; and in the presence of surfactants, including but not limited to a polaxamer, such as Pluronic™ F-68 or F-108 (manufactured by BASF-Wyandotte), which is a block copolymer of ethylene oxide and propylene oxide, a polyoxyethylene alcohol, such as Brij® 30 (manufactured by ICI), a nonoxynol, such as Igepal CO-520® (manufactured by GAF), and Tetronic™ 908. In the presence of such stabilizers and surfactants, the powder produced by spray drying can be rehydrated to form pharmaceutically acceptable drug nanoparticle formulations with particle size of less than about 5000 nm, preferably less than about 1000 nm, more preferably less than about 400 nm, and most preferably less than about 250 nm. A surface modifier adsorbed on the surface of the nanoparticle is preferably included in the nanoparticle production as well.

The present invention is also related to spray drying solutions with different process parameters, including suitable matrix material/agent concentration in the composite mixture, drying temperature, residence time of the composite mixture in the spray dryer, solvent and the presence of surfactant to produce the preferred drug nanoparticles. The concentration of the matrix material/agent component of the composite mixture can be any concentration to the extent that the composite mixture remains atomizable and the matrix forms. By being atomizable, the composite mixture must be pumpable, which is consistent with the composite mixture having a viscosity of no more than about 300 cp,

more preferably no more than about 200 cp, yet more preferably no more than 100 cp. Other components of the composite mixture can be included as discussed herein, to the extent that they do not negatively impact on the ability of the composite mixture to be  
5 atomized, as discussed with respect to the matrix material/agent component. Suitable drying temperatures are those that provide for adequate drying such that the nanoparticles are formed, and of a temperature range that the agent does not become inactivated or substantially inactivated. By "not substantially inactivated," it is  
10 intended that the nanoparticle-form of the agent retains adequate activity for its intended use, as in a drug or a catalyst, even though some activity may have been lost in the spray-drying process. Accordingly, in one embodiment of the present invention, drying temperatures are less than about 275°C, preferably about 200°C,  
15 more preferably about 150°C. In another embodiment, the drying temperatures are less than about 150°C, preferably about 125°C, or 90°C, or 75°C, or 50°C. In yet another embodiment of the present invention, a spray drying process incorporates a combination of different temperatures as herein discussed, or a gradient of such  
20 temperatures, or any combination thereof. Suitable residence times are those that are sufficiently short so as to prevent phase separation of the components of the composite mixture in the spray dryer. Preferably, suitable residence times are less than about 25 seconds, more preferably less than about 15 seconds, yet more  
25 preferably less than about 10 seconds.

Preferred surface modifiers can be low molecular weight polymers (molecular weight less than about 2000) including nonionic and ionic surfactants; natural products and various polymers, and

high molecular weight (molecular weight less than about 20,000 to about 40,000) steric stabilizers including polyvinyl alcohol-polyvinyl acetate copolymers, for example. The surface modifiers preferably do not chemically react with the agent or itself.

- 5        Representative nanocomposite host matrices for the drug include without limitation carbohydrates including sugars, e.g., glucose, fructose, lactose, mannitol, sucrose, maltose, trehalose, sorbitol, mannitol, and mannose; celluloses, e.g., cellulose acetate, cellulose acetate phthalate, carboxymethyl cellulose, ethyl cellulose,
- 10        carboxymethyl cellulose calcium or sodium, carboxymethyl cellulose sodium, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose phthalate and noncrystalline cellulose; and other suitable carbohydrates, such as starch and arabinogalactose; suitable proteins, e.g., collagens, zein, and gelatin;
- 15        inorganic salts, e.g., sodium chloride, potassium chloride, sodium bisulfite, sodium metabisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, sodium benzoate, calcium stearate, calcium carbonate, barium sulfate, sodium salicylate, sulfathiazole sodium salt, and magnesia salts, alumina salts, and magnesia-
- 20        alumina salts, formed with aluminum hydroxide, for example; natural polysaccharides, e.g., gum arabic (acacia), gum ghatti, karaya, tragacanth, locust bean, guar and xanthan gum; water-soluble resins, e.g., polyvinylpyrrolidone, polyvinyl alcohol, and polyacrylic acid; water-insoluble resins, e.g., polyethylene, polymethacrylate,
- 25        polyamide (nylon), and poly (ethylene-vinyl acetate); enteric resins, e.g., shellac; lipids, e.g., a wax, natural and synthetic phospholipids, positively and negatively charged phospholipids, glyceryl esters, paraffin, carnauba, spermaceti, beeswax, steric acid, stearyl alcohol

and glycerol stearates. The matrix material can be in the form of a gel, as in, for example, alumina-magnesia gels, aluminum hydroxide gel and magnesia gel. Resins useful in the context of the present invention are high polymers of natural or synthetic origin, including  
5 those set forth above. Suitable lipids useful in the context of the present invention form porous solid structures at room temperature (about 25°C), more preferably at about 50°C, yet more preferably at about 100°C, and even more preferably at about 150°C.

Nanocomposite host matrices particularly useful in the present  
10 invention are water-soluble sugars such as sucrose, D(+)-lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbitol, D(+)-glucose and D-mannitol; stabilizers such as polyvinyl alcohol-polyvinyl acetate copolymers; and surfactants such as Pluronic™ F-68, Brij® 30, Igepal CO-520® and Tetronic™ 908. The amount of a sugar in the  
15 nanocomposite particles can vary from about 10 to 90%, preferably 30 to 90%, more preferably 40 to 80%, and most preferably 50 to 70% by weight based on the total weight of the drug and sugar.

Examples of some representative surface modifiers are gelatin, casein, phospholipids, stearic acid, gum acacia, cholesterol,  
20 benzalkonium chloride, calcium stearate, magnesium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl esters, e.g., macrogol esters such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, the  
25 commercially available Tweens™, such as Tween 80 having formula weight 1309.68 (purchased from Aldrich Chemical Co., Inc., Catalog # 27,436-4) polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphate, sodium dodecyl sulfate,

carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propymethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and

5 polyvinylpyrrolidone (PVP). A detailed description of these surface modifiers is given in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986.

10 More specifically suitable surface modifiers include polyvinylpyrrolidinone, tyloxapol, polaxamers such as Pluronic™ F-68 and F-108 (manufactured by BASF-Wyandotte), which are block copolymers of ethylene oxide and propylene oxide, and polyoxamines such as Tetronic™ 908 (manufactured by BASF), which is a

15 tetrafunctional block copolymer derived from subsequent addition of propylene oxide and ethylene oxide to ethylenediamine; dextran, lecithin, dialkyl esters of sodium sulfosuccinic acid, such as Aerosol OT™ (manufactured by American Cyanimid), which is a dioctyl ester of sodium sulfosuccinic acid, i.e., docusate, a sodium lauryl sulfate,

20 such as Duponol™ P (manufactured by DuPont), an alkyl aryl polyester sulfonate, such as Triton™ X-200 (manufactured by Rohm and Haas), a polyoxyethylene sorbitan fatty acid ester, i.e., a polysorbate, such as Tween™ (manufactured by ICI Specialty Chemicals), and polyethylene glycols, such as Carbowax™ 3350 and

25 934 (manufactured by Union Carbide). Surface modifiers which have been particularly useful include Tetronic 908, the Tweens™, and Pluronic F-68. Other useful surface modifiers include: decanoyl-N-methylglucamide, n-decyl  $\beta$ -D-glucopyranoside, n-decyl

*$\beta$ -D-maltopyranoside, n-dodecyl  $\beta$ -D-glucopyranoside, n-dodecyl  $\beta$ -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl  $\beta$ -D-glucopyranoside, n-heptyl  $\beta$ -D-thioglucoside, n-hexyl  $\beta$ -D-glucopyranoside, nananoyl-N-methylglucamide, n-nonyl  $\beta$ -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl  $\beta$ -D-glucopyranoside, and n-octyl  $\beta$ -D-thioglucopyranoside.*

Surface modifiers useful in the present invention are Pluronic™ F-68 (a nonionic solid copolymer of ethylene oxide and propylene oxide), and Tetronic™ 908 (a solid nonionic tetrafunctional block copolymer derived from subsequent addition of propylene oxide and ethylene oxide to ethylenediamine). The relative amount of therapeutic or diagnostic agent and surface modifier can vary widely and the optimal amount of surface modifier can depend, for example, upon the therapeutic or diagnostic agent and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the hydrophilic-lipophilic balance (HLB) of the stabilizer, the surface tension of water solutions of the stabilizer and the melting point of the stabilizer.

According to the present invention, a method for the preparation of a nanoparticle composition includes dissolving a therapeutic or diagnostic agent, optionally a nanocomposite host material, and a surface modifier in a suitable solvent. The resulting solution is atomized into droplets and these droplets are converted into solid particles in a horizontal spray dryer. If a surface modifier or polymeric stabilizer is not present in the as-sprayed particles, it can be admixed thereafter. The liquid medium, especially water, can serve as the pharmaceutically acceptable carrier. The method preferably is carried out under aseptic conditions.

As discussed herein, the particle size corresponds to a number median particle size as measured by the conventional particle size measuring techniques, such as laser light scattering methods. A median particle size means that at least about 50% of the particles have a number average particle size of the specified size when measured by the above-mentioned techniques, which defines the term " $d_{50}$ ". Accordingly, a "median particle size of less than about 5000 nm" means that at least 50% of the particles have a number average particle size of less than about 5000 nm. In a preferred embodiment of the invention, the median particle size is less than about 1000 nm, more preferably less than about 400 nm, yet more preferably less than about 300 nm, and most preferably less than about 250 nm. It is preferred that at least about 95%, defining " $d_{95}$ " and, more preferably, at least about 99%, defining " $d_{99}$ " of particles have a median particle size of less than about 400 nm.

The surface modifier, if not present in the spray dried powder, must be added to the dispersing liquid medium in which the therapeutic or diagnostic agent is essentially insoluble to form a stable formulation. The concentration of the therapeutic or diagnostic agent in the liquid medium can vary from about 0 to about 60%, and preferably from about 5 to about 30% (w/w). The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably from about 1 to about 75%, more preferably about 10 to about 60%, and most preferably about 10 to about 30% by weight of the total weight of the drug and the modifier.

Nanocomposite host materials particularly useful in the present invention are water-soluble sugars such as sucrose, D(+) -lactose

monohydrate,  $\beta$ -D-lactose, L(-)-sorbitol, D(+)-glucose and D-mannitol; stabilizers such as polyvinyl alcohol-polyvinyl acetate copolymers; surfactants such as Pluronic™ F-68, Brij® 30, Igepal CO-520® and Tetronic™ 908. The amount of host materials in the  
5 nanocomposite particles can vary from about 10 to about 90%, preferably about 30 to about 90%, more preferably about 40 to about 80%, and most preferably about 50 to about 70% by weight based on the total weight of the drug and host materials.

Among the therapeutic agents which satisfy the matrix mediated  
10 synthesis of nanoparticles are any agents used to treat a disease or condition, such as, but not limited to analgesic and antiinflammatory agents including aspirin, naproxen, indomethacin, ibuprofen, fenoprofen and acetaminophen; antibiotic agents including  
15 penicillins, tetracyclines, aminoglycoside antibiotics, and clindamycin; immunosuppressive agents, immunostimulatory agents, antifungal agents, antiviral agents, antineoplastic agents, anticancer agents, odor masking agents, insect repelling agents, peptides, immune reagents, anesthetic agents, antiseptic agents, antihistamine agents, antioxidants, antidiabetic agents, antiepileptic agents, muscle  
20 relaxants, stimulants, vitamins, hormones, cough suppressants, anti-HIV and anti-AIDS agents, or a combination of any of the foregoing. Such therapeutic agents can be peptides, proteins, nucleic acids of any suitable size, carbohydrates, lipids, steroids, and the like, and combinations thereof as covalently combined or by admixture. Such  
25 therapeutic agents can also be tissue growth factors, liposaccharide complexing agents, and the like. The amount of drug in the nanocomposite particles can vary from about 10 to about 90%, preferably about 10 to about 70%, more preferably about 20 to



about 60%, and most preferably about 30 to about 50% by weight based on the total weight of the drug and host materials.

The composite approach can offer a number of advantages in terms of reducing the particle size, yield, production rate and phase distribution flexibility. Since sugars such as sucrose, D(+)-lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbitol, D(+)-glucose and D-mannitol, surfactants such as Pluronic F-68, and Tetronic 908, and stabilizers polyvinyl alcohol-polyvinyl acetate copolymers are highly soluble in water, but not the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate and naproxen crystals, dispersing the composite particles in water with about 0.03 wt.% Pluronic™ F-68 and removing the aqueous sugar solutions result in the formation of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanocrystals. These crystalline nanoparticles with surface modified by Pluronic™ F-68, Tetronic 908, and Igepal CO-520® maintain a median particle size of less than about 400 nm. The concentration of the therapeutic or diagnostic agent in the liquid medium can vary from about 0 to about 60%, and preferably from about 5 to about 30% (w/w). The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably from about 1 to about 75%, more preferably about 10 to about 60%, and most preferably about 0 to about 30% by weight of the total weight of the drug and the modifier.

The nanoparticles that are synthesized by the method of the invention, which include a therapeutic or diagnostic agent (collectively referred to as drug nanoparticles), can be administered orally, topically, rectally, nasally, vaginally, by inhalation, for example by use of an aerosol, or parenterally, i.e. intramuscularly,

subcutaneously, intraperitoneally, intraventricularly, or intravenously. The drug nanoparticles are administered alone, or they are combined with a pharmaceutically-acceptable carrier or excipient according to standard pharmaceutical practice. For the oral mode of

5 administration, the drug nanoparticles are used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and suspensions, and the like. In the case of tablets, carriers that are used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants, such as starch, and

10 lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the polynucleotide compositions are

15 combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents are added. For parenteral administration, sterile suspensions of the drug nanoparticles are usually prepared, and the pH of the suspensions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes

20 are controlled to render the preparation isotonic. For ocular administration, ointments or droppable liquids are delivered by ocular delivery systems known to the art, such as applicators or eye droppers. Such compositions include mucomimetics, such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or

25 poly(vinyl alcohol), preservatives, such as sorbic acid, EDTA or benzylalkonium chloride, and the usual quantities of diluents and/or carriers. For pulmonary administration, diluents and/or carriers are selected as appropriate for formation of an aerosol.

Generally, the drug nanoparticles are administered in an effective amount. An effective amount is an amount effective to either (1) reduce the symptoms of the disease sought to be treated or (2) induce a pharmacological change relevant to treating or preventing or  
5 diagnosing the disease sought to be treated or prevented or diagnosed.

The following examples further illustrate the present invention but, of course, should not be construed as in any way limiting its  
10 scope.

#### Example 1

This example illustrates spray drying equipment as used in the context of the present invention.

15 Spray drying equipment used for demonstrations of the present invention is schematically displayed in Fig. 1. The spray drying equipment consists of a feed delivery system, a nebulizer, a glass drying tube of about 3 meters in length with 5-temperature zones,  $T_1$  to  $T_5$ , a filter to collect the powder, a liquid  $N_2$  trap for the solvent,  
20 and a vacuum pump. This spray dryer is similar to parallel (cocurrent) air flow drying systems, such as flash dryers. The drying cycle in the displayed spray dryer particularly occurs in one unit (single-stage conveyor).

For the applications concerning generation of drug nanoparticles,  
25 the 5-temperature zones,  $T_1$  to  $T_5$ , ranged in temperature from about  $75^\circ\text{C}$  to about  $250^\circ\text{C}$ . The following examples provide data and detail concerning the temperatures actually used, the position of the various regions of a given temperature within the spray dryer,

including recitation of a gradient of temperature, all with respect to  $T_1$  to  $T_5$ . In particular, see Tables 3 to 8 and associated text. The residence time of the composite material in the spray dryer until it emerges as nanocomposite ranges up to 10 seconds.

- 5        Other configurations of the spray dryer that are useful in the context of the present invention also include multistage units for drying solids that have high solvent vapor content and contain large amounts of bound solvent.

10

### Example 2

This example illustrates one embodiment of the present invention, whereby nanoparticles were generated using the spray drying equipment of Example 1.

- 15        Solutions with ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (manufactured by Nanosystems, Inc., Collegeville, PA):sugar (1:2 and 1:9 wt.%) were prepared by dissolving ethyl 3,5-diacetamido-2,4,6-triiodobenzoate and one of the following sugars; sucrose, D(+)-lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbose, D(+)-glucose and D-mannitol in DMSO and water by
- 20        the following procedure: In a 200 mL bottle, 5 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate was dissolved in 100 mL DMSO. To this solution, 10 g of one of the aforementioned sugars was dissolved in 10 mL water, and was added drop by drop, and resulted in a clear solution. These ethyl 3,5-diacetamido-2,4,6-
- 25        triiodobenzoate:sugar solutions were sonicated using a probe sonicator (Model # VC500; Sonics & Materials Inc.) for 10 minutes and then atomized with an ultrasonic nebulizer (Model # 099HD; Devilbiss Co.) operating at a solution flow rate of 10 to 20 mL/hour

and a nitrogen pressure of 0.10 to 0.25 MPa using the spray dryer described in Example 1. The atomized droplets (average diameter 1-5  $\mu\text{m}$ ) were transported through the glass drying tube with 5-temperature zones heated between 60°C and 250°C. The  $T_5$  zone of the tube was heated above the flash points of DMSO and water. The moistened solid was suspended in a finely divided state in a medium velocity (20 to 100  $\text{m} \cdot \text{s}^{-1}$ ) hot nitrogen stream. The resulting dried, fine particulate material, i.e., the nanocomposite powder, was collected in the filter by maintaining a filter pressure draft of about 0.01 to 0.05 MPa by using the vacuum pump, as depicted in Fig. 1. The residence time for a droplet in the glass tube was 2 to 10 seconds.

The spray dried nanocomposite powders were dispersed in water with surfactant by sonication using an ultrasonic power supply having a frequency of either 20 or 80 kHz for about 1 to about 5 min. From particle size analysis, it was determined that these nanocomposite powders, when rehydrated in water with 0.1% (w/v) Pluronic™ F-68 surfactant, yielded ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle formulations with median particle diameters of 160 to 275 nm. Table 1 lists the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:sugar nanocomposites spray dried, and the particle size distribution of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate-containing particles, wherein "CMP-1" means ethyl 3,5-diacetamido-2,4,6-triiodobenzoate.

Table 1

Amount of CMP-1 (g)	Amount of Sugar (g)	Sugar	Particle Size** (nm)		
			d <sub>10</sub> **	d <sub>50</sub>	d <sub>90</sub>
5	10	Sucrose	138	191	256
5	10	$\beta$ -D-lactose	153	190	248
5	10	D(+)-glucose	204	274	365
5	10	L(-)-sorbitol	198	240	297
5	10	D(+)-lactose monohydrate	205	277	373
5	10	D-mannitol	204	275	369
1	9	$\beta$ -D-lactose	119	160	219

\*\* measured using Horiba LA-900; \*\*diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

Ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:sucrose (1:2 wt. %) nanocomposite particles were analyzed by scanning and transmission electron microscopy, SEM and TEM, respectively, and energy dispersive analysis by x-ray. The SEM micrographs (not shown) showed agglomerates of composite particles, whereas the TEM micrographs (not shown) showed the distribution of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate particles (which are electron dense, thus darker structures) and sucrose particles (less electron dense relative to the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate, thus lighter structures) to be uniform in the nanocomposite. The ethyl 3,5-diacetamido-2,4,6-triiodobenzoate particle size as seen in the micrographs varied from about 15 nm to about 45 nm, whereas the sucrose particle size ranged from about 90 nm to about 200 nm. The energy dispersive analysis by x-ray demonstrated the presence

of iodine atoms of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate throughout the composite particles, as can be seen in the graph of Fig. 3, wherein the x-axis is labelled as keV for x-ray energy levels and peaks are labeled to identify those associated with carbon (C),  
5 oxygen (O), iron (Fe), copper (Cu), and iodine (I).

### Example 3

This example illustrates production of nanoparticles using the present invention.

10 Solutions with ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:sugar (1:2 wt.%) were prepared by dissolving ethyl 3,5-diacetamido-2,4,6-triiodobenzoate and one of the following sugars; D(+) -lactose monohydrate,  $\beta$ -D-lactose, and D-mannitol in a DMSO-water mixture as described in Example 2. To scale-up the powder production rate  
15 and to assess the effect of droplet size on the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate particle size, a pressure atomizer was used. The diameter of droplets generated from the pressure atomizer was 10 to 30  $\mu$ m, whereas the solution flow rate was varied between 1.5 to 3 mL/min. These atomized droplets were  
20 transported through the glass tubes of the spray drying equipment with 5-temperature zones as depicted in Fig. 1. The maximum temperature of the glass tube was 250°C. Evaporation of water and DMSO within the tube resulted in air-born ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:sugar nanocomposite  
25 particles. These particles were collected in a finely woven Gortex bag (Grade P-80; purchased from Standard Filter Co).

These nanocomposite powders were dispersed in water with 2.5% (w/v) Pluronic F-68. By centrifuging the colloidal dispersion

for about 60 minutes, removing the supernatant liquid containing the sugar, and repeating the process for at least 3 times, the drug nanoparticle dispersion was prepared. From particle size analysis, it was determined that these nanoparticles dispersed in water with 2.5% (w/v) Pluronic F-68 surfactant, yielded drug formulations with median particle diameters of 195 to 275 nm. Table 2 lists the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:sugar nanocomposites spray dried, and the particle size distribution of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate. Zeta potential measurement of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate ("CMP-1") dispersed in 0.04% (W/V) Pluronic F-68 using a Malvern ZetaSizer indicated the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate particles were negatively charged (zeta potential = -16.1 mV).

Table 2

Amount of CMP-1 (g)	Amount of Sugar (g)	Sugar	Particle Size** (nm)		
			d <sub>10</sub> **	d <sub>50</sub>	d <sub>90</sub>
5	10	D-Mannitol	208	282	369
5	10	$\beta$ -D-lactose	153	195	248
5	10	D(+)-glucose monohydrate	214	280	365

\*\* measured using Horiba LA-900; \*\*diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

#### Example 4

This example illustrates production of nanoparticles using the present invention.

Solutions with 1 to 20 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate per 100 mL 1-methyl-2-pyrrolidinone (12 MPO) were



prepared by the following procedure. In a 250 mL beaker, 5 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate and 100 mL 12 MPO and 1.5 g were added, and sonicated for 15 minutes. Sonication accelerated the dissolution of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in 12 MPO. Also, solutions of 5 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate per 100 mL 12 MPO with either 0.15 g or 1.5 g Pluronic™ F-68 were prepared as described above. These ethyl 3,5-diacetamido-2,4,6-triiodobenzoate solutions were spray dried using the spray drier described in Example 1. The maximum drying temperature was 250°C to produce the nanoparticles. The as-produced fine powders were collected in a filter bag.

Tables 3-6 list the particle sizes of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate spray dried from the aforementioned ethyl 3,5-diacetamido-2,4,6-triiodobenzoate ("CMP-1") per 100 mL 12 MPO solutions, as well as other parameters measured.

Table 3

Amount of CMP-1 (g)	Solvent*	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub> , T <sub>5</sub>	Particle Size** (nm) d <sub>10</sub> d <sub>50</sub> d <sub>90</sub>
1	12 MPO	125, 175, 200, 250, 125	304
2.5	12 MPO	125, 175, 200, 250, 125	387
5	12 MPO	125, 175, 200, 250, 125	387
10	12 MPO	125, 175, 200, 250, 125	537
20	12 MPO	125, 175, 200, 250, 125	591

\* Volume of solvent added was 100 mL;

\*\* measured with a Malvern Zetasizer 4; \*\*diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

Table 4

Amount of CMP-1 (g)	Solvent •	Pluronic F-78 (wt%) <sup>*</sup>	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub> , T <sub>5</sub>	Particle Size <sup>**</sup> (nm)		
				d <sub>10</sub> <sup>**</sup>	d <sub>50</sub>	d <sub>90</sub>
20	12 MPO	--	125, 175, 200, 250, 125	591		
20	12 MPO	--	125, 175, 200, 250, 60	615		
10	12 MPO	0.03	125, 175, 200, 250, 125	407		
10	12 MPO	0.03	125, 175, 200, 250, 60	782		

<sup>\*</sup> Volume of solvent added was 100 mL; <sup>\*</sup>with respect to 100 mL solvent;

<sup>\*\*</sup> measured with a Malvern Zetasizer 4; <sup>\*\*</sup>diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

Table 5

Amount of CMP-1 (g)	Solvent •	Pluronic F-78 (wt%) <sup>*</sup>	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub> , T <sub>5</sub>	Particle Size <sup>**</sup> (nm)		
				d <sub>10</sub> <sup>**</sup>	d <sub>50</sub>	d <sub>90</sub>
5	12 MPO	—	125, 175, 200, 250, 125	387		
5	12 MPO	0.15	125, 175, 200, 250, 125	253	351	965
5	12 MPO	1.5	125, 175, 200, 250, 125	238	324	858

<sup>\*</sup> Volume of solvent added was 100 mL; <sup>\*</sup>with respect to 100 mL solvent;

<sup>\*\*</sup> measured with a Malvern Zetasizer 4; <sup>\*\*</sup>diameter on volume %.

Table 6

Amount of CMP-1 (g)	Solvent*	Pluronic F-78 (wt%)*	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub> , T <sub>5</sub>	Particle Size** (nm)		
				d <sub>10</sub> **	d <sub>50</sub>	d <sub>90</sub>
5	DMSO	—	125, 175, 200, 250, 125	249	347	1020
10	DMSO	--	125, 175, 200, 250, 125	590		
5	DMSO	0.15	125, 175, 200, 250, 125	242	335	1140
5	DMSO	1.5	125, 175, 200, 250, 125	240	310	894
5	DMSO	5.0	125, 175, 200, 250, 125	227	205	394

\* Volume of solvent added was 100 mL; \*with respect to 100 mL solvent;

\*\* measured with a Malvern Zetasizer 4; \*\*diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

The spray drying temperature ( $T_5 = 60^\circ\text{C}$  or  $125^\circ\text{C}$ ) played a key role in the final particle size. When the final drying temperature was  $125^\circ\text{C}$ , properly dried finer particles were produced from ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in 12 MPO solutions with and without Pluronic™ F-68 (Table 4). Also, increasing the concentration of the surfactant in ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in 12 MPO and ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in DMSO

solutions decreased the median particle size of the spray dried powders (Tables 5 and 6).

#### Example 5

5        This example illustrates production of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle/Pluronic™ F-68  
formulation, which is produced in the context of the present  
invention.

10        An ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle  
formulation was prepared by dispersing 4 g of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate:βD-Lactose (1:2 wt.%)  
nanocomposite (prepared as in Example 2) in 20 mL of 1% (w/v)  
Pluronic™ F-68 in water (pH 4.20). About 1 to 10 mg 1-octanol was  
15        added as a defoaming agent. The nanocomposite mixture was  
sonicated for 5 to 10 minutes to form a stable and homogeneous  
ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle formulation.  
The median particle size of the dispersion measured by the laser light  
scattering method using Horiba LA-900 was 255 nm, and all the  
particles in the dispersion maintained a size of less than 400 nm.

20

#### Example 6

25        This example illustrates production of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle/Igepal CO-520®  
formulation 1, which is produced in the context of the present  
invention.

A ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle  
formulation was prepared by dispersing 4 g of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate:βD-Lactose (1:2 wt.%)

nanocomposite (prepared as in Example 2) in 20 mL of 1% (w/v) 4-(C<sub>9</sub>H<sub>19</sub>)C<sub>6</sub>H<sub>4</sub>O(CH<sub>2</sub>CH<sub>2</sub>O)<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>OH (Igepal CO-520®; purchased from Aldrich Chemical Co., Inc., Catalog # 23,864-3) in water.

About 1 to 10 mg 1-octanol was added as a defoaming agent. As described in Example 5, the formulation was sonicated and the particle size was measured. The median particle size of the dispersion was 205 nm and all the particles in the dispersion maintained a size of less than 400 nm.

#### 10 Example 7

This example illustrates production of the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle/Igepal CO-520® formulation 2, which is produced in the context of the present invention.

15 A CMP-1 nanoparticle formulation was prepared by dispersing 4 g of the ethyl 3,5-diacetamido-2,4,6-triiodobenzoate:D-Mannitol (1:2 wt.%) nanocomposite (prepared as in Example 2) in 20 mL of 1% (w/v) Igepal CO-520® in water. About 1 to 10 mg 1-octanol was added as a defoaming agent. As described in example 6, the  
20 formulation was sonicated and the particle size was measured. The median particle size of the dispersion was 295 nm, and all the particles in the dispersion maintained a size less than 400 nm.

### Example 8

This example illustrates production of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle/Brij® 30  
formulation, which is produced in the context of the present  
5 invention.

A ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle  
formulation was prepared by dispersing 4 g of the ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate:β-D-Lactose (1:2 wt.%)  
nanocomposite (prepared as in Example 2) in 20 mL of 1% (w/v)  
10 C<sub>12</sub>H<sub>25</sub>(OCH<sub>2</sub>CH<sub>2</sub>)<sub>4</sub>OH (Brij® 30; purchased from Aldrich Chemical  
Co., Inc., Catalog # 23,598-9) solution in water. About 1 to 10 mg  
1-octanol was added as a defoaming agent. As described in  
example 7, the formulation was sonicated and the particle size was  
measured. The median particle size of the dispersion was 225 nm  
15 and all the particles in the dispersion maintained a size of less than  
400 nm.

### Example 9

This example illustrates production of the ethyl  
20 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle/Tetronic™ 908  
formulation, which is produced in the context of the present  
invention.

A ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticle  
formulation was prepared by dispersing 4 g of the ethyl  
25 3,5-diacetamido-2,4,6-triiodobenzoate:β-D-Lactose (1:2 wt.%)  
nanocomposite (prepared as in Example 2) in 20 mL of 1% (w/v)  
Tetronic™ 908 in water (pH = 4.20). About 1 to 10 mg 1-octanol  
was added as a defoaming agent. As described in example 7, the

formulation was sonicated and the particle size was measured. The median particle size of the dispersion was 210 nm and all the particles of the dispersion maintained a size of less than 400 nm.

5

#### Example 10

This example illustrates certain applications of the present invention for the preparation of naproxen-containing nanoparticles.

Solutions of naproxen and host matrices such as ethyl cellulose, sucrose, glucose, and D-mannitol in alcohol, water, DMF, and DMSO  
10 were spray dried using the spray dryer described in Example 1. The size of the atomized droplets was about 1-5  $\mu\text{m}$ , and the maximum spray drying temperature was 150°C. Table 7 shows the naproxen nanocomposite formulations prepared by this method. The particle  
15 size was measured using a Shimadzu SALD-2001 laser diffraction particle size analyzer. Naproxen nanoparticle formulations were prepared by dispersing the nanocomposite powders in water saturated with naproxen and 0.1% (W/V) Brij<sup>®</sup> 30, at pH 2.5 and sonicating for 5 min. The temperature of these dispersions during preparation and particle size analysis were maintained below 10°C.

Table 7

	Composition	Solvent	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub> , T <sub>5</sub>	Particle Size Distribution (nm) d <sub>10</sub> d <sub>50</sub> d <sub>90</sub>	Crystallite Size (XRD) (nm)
5	5 g Naproxen	200 mL Ethanol	75, 100, 125, 150, 90	878 1225 3125	33.5
10	5 g Naproxen 5 g Ethyl cellulose	200 mL Ethanol	75, 100, 125, 150, 90	----	31.2
15	5 g Naproxen 10 g Sucrose	200 mL Ethanol 40 mL H <sub>2</sub> O	75, 100, 125, 150, 90	51 91 168	32.0
20	5 g Naproxen 10 g Glucose	200 mL Ethanol 40 mL H <sub>2</sub> O	75, 100, 125, 150, 90	110 170 230	34.0
25	5 g Naproxen 5 g Sucrose	200 mL Ethanol 20 mL H <sub>2</sub> O	75, 100, 125, 150, 90	165 230 395	32.4
30	5 g Naproxen 10 g Sucrose	100 mL DMF 20 mL H <sub>2</sub> O	75, 100, 125, 150, 90	65 110 210	32.3
	5 g Naproxen 10 g D-Mannitol	100 mL DMSO	75, 100, 125, 150, 90	65 110 210	33.0

\*\* diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

As indicated in Table 7, naproxen nanoparticles of less than 400 nm resulted depending on the sugar selected as matrix. In particular, sucrose, glucose, and D-mannitol provided nanoparticles of less than 400 nm.



An x-ray diffraction analysis using standard methods was done for the 5 g naproxen/5 g ethyl cellulose nanocomposite, which was prepared using the spray drying equipment described in Example 1. The graph of Fig. 9, wherein the y-axis is labeled Relative Intensity and the x-axis is labeled Degrees Two Theta (Cu K $\alpha$ ), displays the x-ray diffraction ("XRD") result both for the naproxen/ethyl cellulose particles as well as for particles prepared from a solution of ethyl cellulose alone. The crystallite size of naproxen is measured from the full-width at half-maximum of the naproxen peak at 19 degrees two theta using Scherer's formula (see Cullity, *Elements of X-Ray Diffraction* (2d ed., Addison-Wesley Publishing Company, Inc., 1978), page 102). Accordingly, as reported in Table 7, the naproxen crystallite size ranges from about 31 to 34 nm.

#### Example 11

This example illustrates production of naproxen nanoparticles using various matrices.

Solutions of naproxen and host matrices such as sucrose, polyvinyl alcohol-polyvinyl acetate (PVA-PVC) copolymer, and Tetronic 908 in alcohol and water were spray dried using a commercial NIRO atomizer. Air was used as the carrier gas; the air pressure was 55 psi. The inlet and outlet air temperatures were 115° and 70°C, respectively. Table 8 lists the naproxen nanocomposite formulations prepared by this method. The naproxen dispersions were prepared as described in Example 10.

Table 8

	Composition	Solvent	Drying Temperature Gradient (°C) T <sub>1</sub> , T <sub>2</sub>	Particle Size Distribution (nm) d <sub>10</sub> <sup>***</sup> d <sub>50</sub> d <sub>90</sub>			Crystallite Size (XRD) (nm)
				d <sub>10</sub> <sup>***</sup>	d <sub>50</sub>	d <sub>90</sub>	
5	20 g Naproxen 100 g Sugar 10 PVA-PVC	1000 mL Ethanol 400 mL H <sub>2</sub> O	115, 70	61	95	160	28.4
10	10 g Naproxen 100 g Sugar 2 PVA-PVC	1000 mL Ethanol 400 mL H <sub>2</sub> O	115, 70	85	108	168	31.2
15	5 g Naproxen 10 g Sucrose	200 mL Ethanol 40 mL H <sub>2</sub> O	115, 70	88	143	251	32.0
20	10 g Naproxen 100 g Sucrose 10 g Tetronic 908	1000 mL Ethanol 40 mL H <sub>2</sub> O	115, 70	90	162	264	32.4

\*\*\* diameter (%) based on volume distribution, wherein at least about 10%, 50%, or 90%, as indicated, of the particles have the specified number average particle size.

Each of the matrices used in the above-described process to prepare nanoparticles resulted in particles of less than 400 nm.

### Example 12

This example illustrates the effect of varying the concentration of the agent in a solution for the production of drug nanoparticles on the median size of the resultant particles.

Nanoparticles that included ethyl 3,5-diacetamido-2,4,6-triiodobenzoate as the agent were prepared in accordance with the method set forth in Example 2, but wherein the weight of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate included in the solution per

100 mL of 12 MPO varied 2 g to 20 g. Median particle size was measured as noted above. The results are shown in the graph of Fig. 4, wherein the y-axis is labeled Median Particle Size (nm) and the x-axis is labeled Weight of CMP-1 (g) /100 mL 12 MPO, wherein  
5 CMP-1 means ethyl 3,5-diacetamido-2,4,6-triiodobenzoate. The graph clearly shows that increasing the initial concentration of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in the indicated solutions increases the median particle size of the spray dried ethyl 3,5-diacetamido-2,4,6-triiodobenzoate powder.

10

### Example 13

This example illustrates the effect of varying the concentration of surfactant in a solution for the production of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate nanoparticles on the median  
15 size of the resultant particles.

15

Nanoparticles that included ethyl 3,5-diacetamido-2,4,6-triiodobenzoate as the agent were prepared in accordance with the method set forth in Example 2, but wherein the weight of surfactant (Pluronic™ F-68) included in the solution per 100 mL of 12 MPO  
20 varied from 0 g to 1.5 g. Median particle size was measured as noted above. The results are shown in the graph of Fig. 5, wherein the y-axis is labeled Median Particle Size (nm) and the x-axis is labeled Weight of Pluronic™ F-68 (g) /100 mL 12 MPO. The graph clearly shows that increasing the initial concentration of ethyl  
25 3,5-diacetamido-2,4,6-triiodobenzoate in the indicated solutions decreases the median particle size of the spray dried ethyl 3,5-diacetamido-2,4,6-triiodobenzoate powder.

25

#### Example 14

This example illustrates the effect of sonication of spray dried particles in the presence of surfactant to produce nanoparticles.

Some of the powders spray dried from ethyl  
5 3,5-diacetamido-2,4,6-triiodobenzoate in 12 MPO solutions, without  
the surfactant, as in Example 13, were shown via SEM micrographs  
(not shown) to consist of agglomerated small particles. The thus  
spray dried powders were dispersed in water with surfactant using  
an ultrasonic power supply. The results are shown in the graph of  
10 Fig. 6, wherein the y-axis is labeled % In Class and the x-axis is  
labeled Diameter (nm)  $\times 10^3$ . As can be seen in Fig. 6, the median  
particle size of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate (CMP-1)  
spray dried from, in the instance of the particles studied in Fig. 6, a  
2.5 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate in 100 mL 12  
15 MPO solution decreases initially with sonication time, and plateaus  
after about 30 minutes of sonication time.

#### Example 15

This example illustrates the results of an x-ray diffraction analysis  
20 of ethyl 3,5-diacetamido-2,4,6-triiodobenzoate-containing spray-dried  
powders.

Spray dried powders containing 10 g or 5 g ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate per 100 mL 12 MPO were  
prepared in accordance with Example 2. The resulting powders were  
25 analyzed by x-ray diffraction, using standard procedures. As can be  
seen in Fig. 7, wherein the y-axis is labeled Relative Intensity and the  
x-axis is labeled Degrees Two Theta, the x-ray diffraction results  
indicate no compositional differences between the untreated powder

and the spray dried powders prepared from ethyl  
3,5-diacetamido-2,4,6-triiodobenzoate in 12 MPO solutions.

However, for those powders prepared by spray drying solutions of  
5 g ethyl 3,5-diacetamido-2,4,6-triiodobenzoate, 100 mL 12 MPO  
5 and 0 to 1.5 g Pluronic™ F-68, the x-ray diffraction patterns showed  
preferred orientations. As can be seen in Fig. 8, wherein the y-axis  
is labeled Relative Intensity and the x-axis is labeled Degrees Two  
Theta, the intensity peak observed at 8° of two theta increases with  
increasing Pluronic™ F-68 concentration from 0 to 1.5 wt. %. SEM  
10 and TEM micrographs (not shown) showed formation of needle-  
shaped crystals in the presence of Pluronic™ F-68 correlated to the  
preferred orientation.

While this invention has been described with an emphasis upon a  
15 preferred embodiment, it will be obvious to those of ordinary skill in  
the art that variations in the preferred composition and method may  
be used and that it is intended that the invention may be practiced  
otherwise than as specifically described herein. Accordingly, this  
invention includes all modifications encompassed within the spirit  
20 and scope of the invention as defined by the following claims.

**WHAT IS CLAIMED:**

1. A method for synthesizing nanoparticles comprising:
  - (a) combining an agent and a matrix material to form a composite mixture; and
  - (b) spray drying the composite mixture, forming a nanocomposite.
2. The method of claim 1, wherein the agent is a diagnostic, therapeutic, cosmetic, dye, photographic, food, pesticide agent, or metal catalyst.
3. The method of claim 2, wherein the diagnostic agent is ethyl 3,5-diacetamido-2,4,6-triiodobenzoate.
4. The method of claim 2, wherein the therapeutic agent is selected from the group consisting of an antiinflammatory agent, an antibiotic agent, an antifungal agent, an antiviral agent, an antineoplastic agent, an immunosuppressive agent, an immunostimulatory agent, an odor masking agent, an insect repelling agent, an anesthetic agent, an antiseptic agent, an antioxidant, an antihistamine, an antidiabetic agent, an antiepileptic agent, a muscle relaxant, a stimulant, an antiallergic agent, a liposaccharide complexing agent, a vitamin, a hormone, an anticancer agent, and a cough suppressant.
5. The method of claim 4, wherein the antiinflammatory agent is naproxen.
6. The method of claim 1, wherein the nanoparticles have a median size less than about 5000 nm.
7. The method of claim 1, wherein the nanoparticles have a median size less than about 1000 nm.

8. The method of claim 1, wherein the nanoparticles have a median size less than about 400 nm.

9. The method of claim 1, wherein the matrix material comprises a carbohydrate, a protein, an inorganic salt, a resin, or a lipid.

10. The method of claim 9, wherein the carbohydrate is a sugar selected from the group consisting of sucrose, glucose, fructose, mannose, maltose, D(+)-lactose monohydrate,  $\beta$ -D-lactose, L(-)-sorbose, sorbitol, and D-mannitol.

11. The method of claim 9, wherein the carbohydrate is a cellulose selected from the group consisting of cellulose acetate, cellulose acetate phthalate, carboxymethyl cellulose, ethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose phthalate and noncrystalline cellulose.

12. The method of claim 9, wherein the carbohydrate is a natural polysaccharide selected from the group consisting of gum arabic (acacia), gum ghatti, karaya, tragacanth, locust bean, guar and xanthan gum.

13. The method of claim 9, wherein the inorganic salt is selected from the group consisting of sodium chloride, potassium chloride, sodium bisulfite, sodium metabisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, sodium benzoate, calcium stearate, calcium carbonate, barium sulfate, sodium salicylate and sulfathiazole sodium salt.

14. The method of claim 9, wherein the gel is selected from the group consisting of alumina-magnesia gels, aluminum hydroxide gel and magnesia gel.

15. The method of claim 9, wherein the resin is selected from the group consisting of gelatin, starch, polyvinylpyrrolidone, arabinogalactan, polyvinyl alcohol, polyarylic acid, polyethylene, polymethacrylate, polyamide (nylon), poly [ethylene-vinyl acetate], and shellac.

16. The method of claim 9, wherein the lipid is selected from the group consisting of natural and synthetic phospholipids, glyceryl esters, paraffin, camauba, spermaceti, beeswax, steric acid, stearyl alcohol and glycerol stearates.

17. The method of claim 9, wherein the protein is collagen, gelatin or zein.

18. The method of claim 3, wherein the nanoparticles have a median size of from about 160 nm to about 280 nm.

19. The method of claim 4, wherein the antiinflammatory agent is aspirin, naproxen, indomethacin, ibuprofen, fenoprofen or acetaminophen.

20. The method of claim 4, wherein the antibiotic agent is selected from the group of penicillins, tetracyclins, aminoglycoside antibiotics, and clindamycin.

21. The method of claim 19, wherein the antiinflammatory agent is naproxen, the composite mixture comprises sucrose, a polyvinyl alcohol-polyvinyl acetate copolymer, a block copolymer of ethylene oxide and propylene oxide, or a polyoxamine, and the nanoparticles have a median particle size of from about 90 nm to about 185 nm.

22. The method of claim 1, wherein the nanoparticles are formulated as a colloidal suspension, capsule, tablet, or powder.



23. The method of claim 1, wherein the ratio of agent to matrix material in the nanocomposite is from about 10:1 to about less than 1:100.

24. The method of claim 23, wherein the composite mixture is combined with organic or aqueous solvents or a combination thereof.

25. The method of claim 24, further comprising atomizing the composite mixture.

26. The method of claim 25, wherein the atomized composite mixture forms droplets of from about 1  $\mu\text{m}$  to about 50  $\mu\text{m}$ .

27. A pharmaceutical formulation comprising a nanoparticle synthesized in accordance with claim 1 and a pharmaceutical carrier.

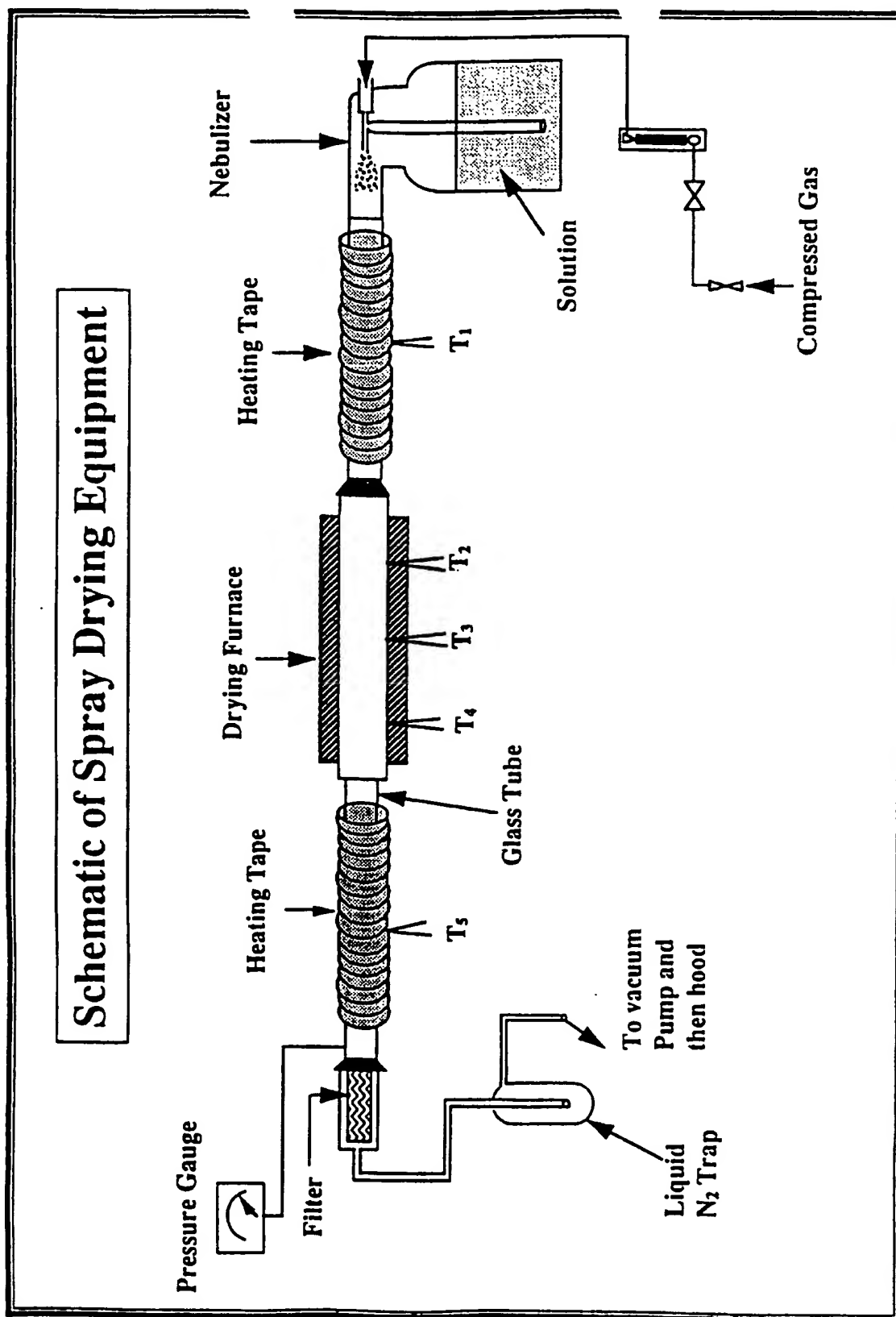


Fig. 1

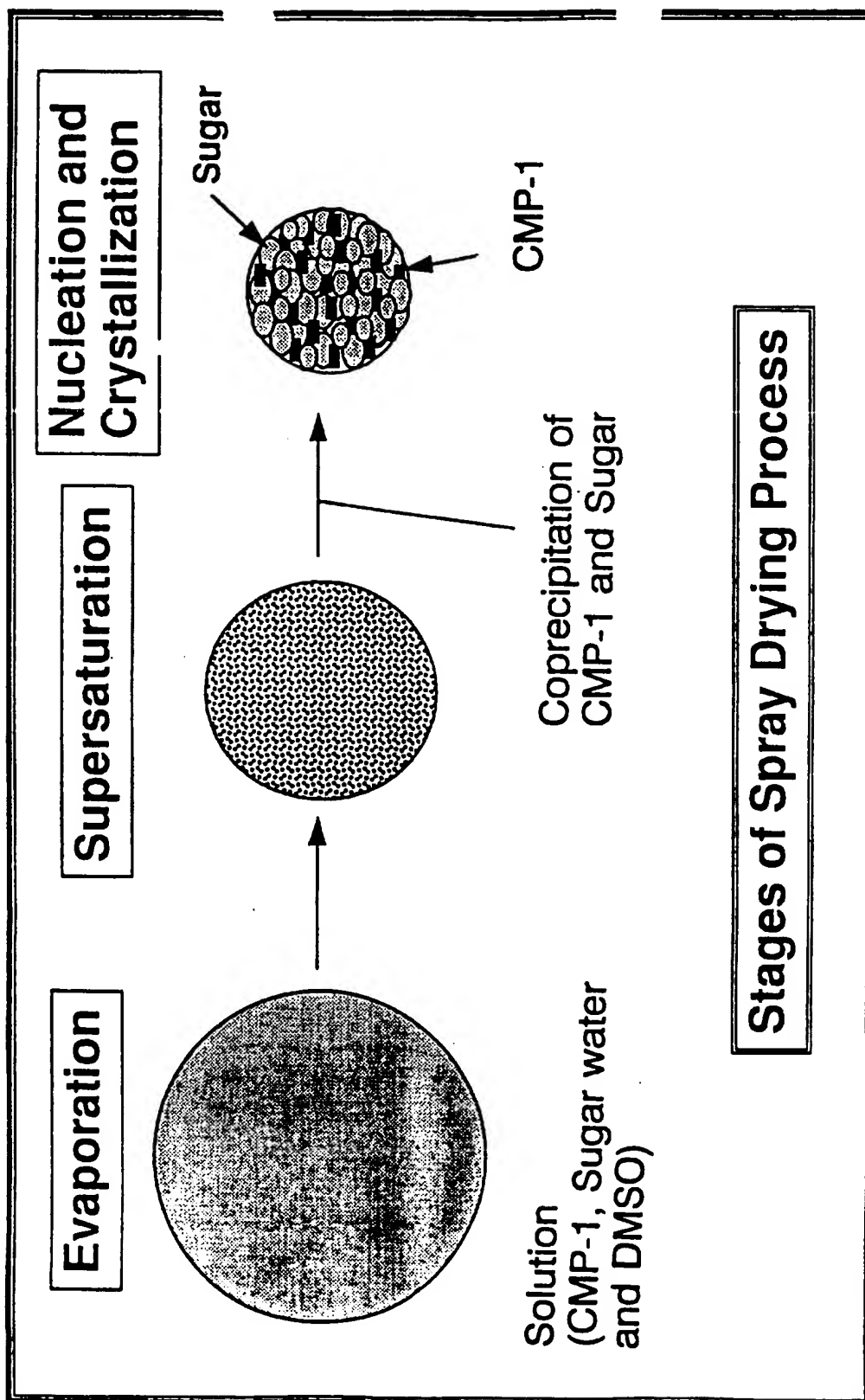


Fig. 2

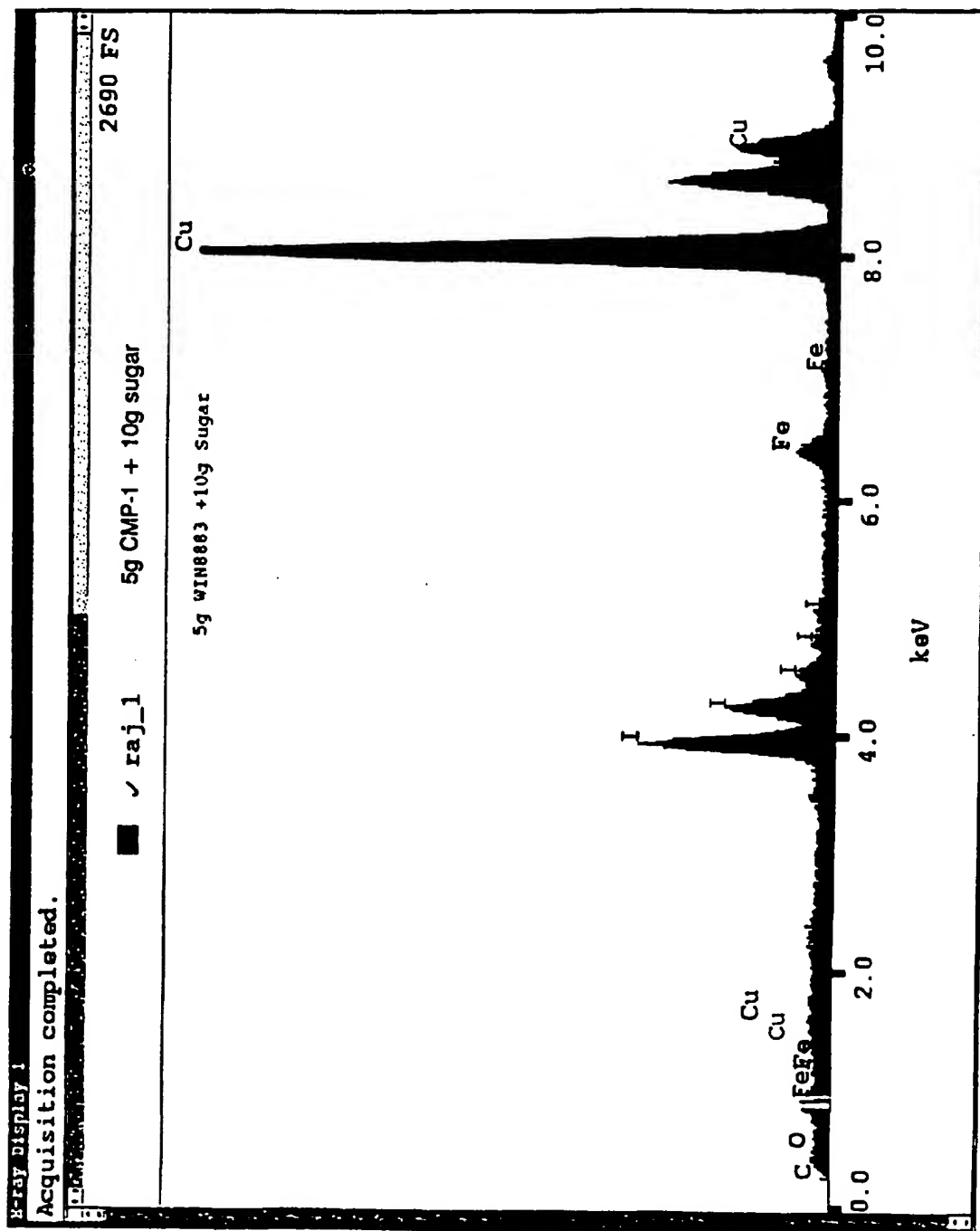


Fig. 3

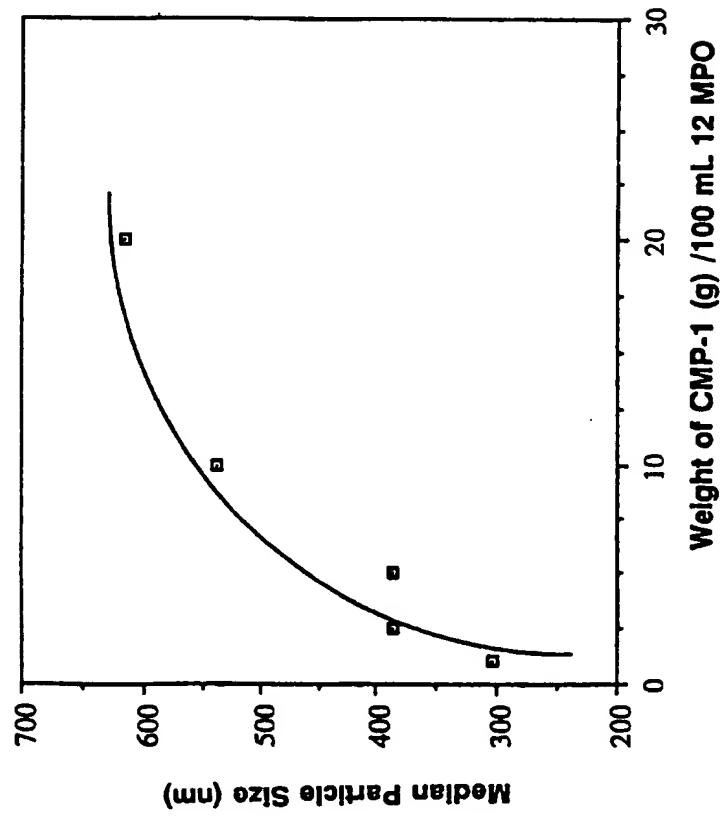


Fig. 4

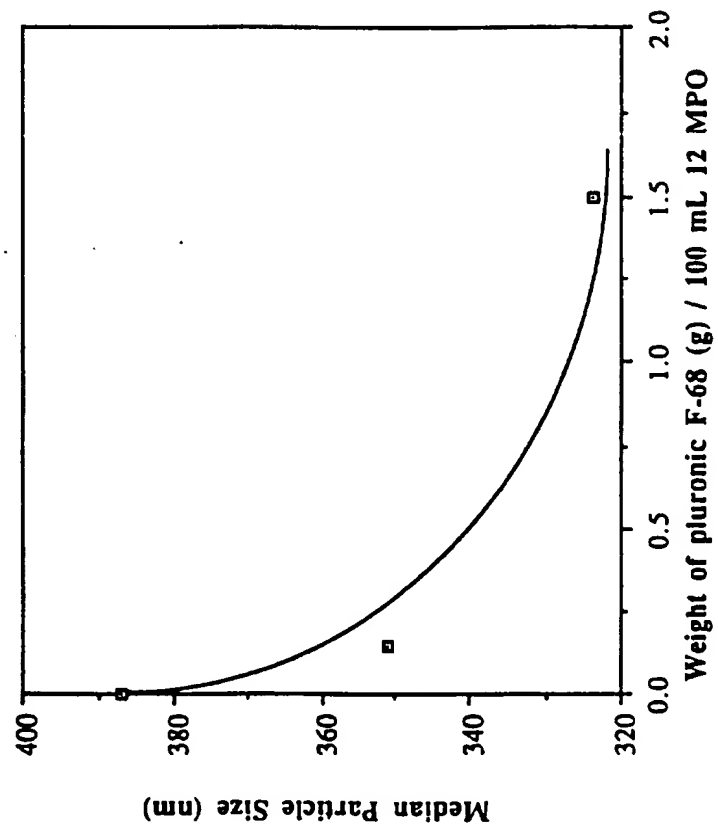


Fig. 5

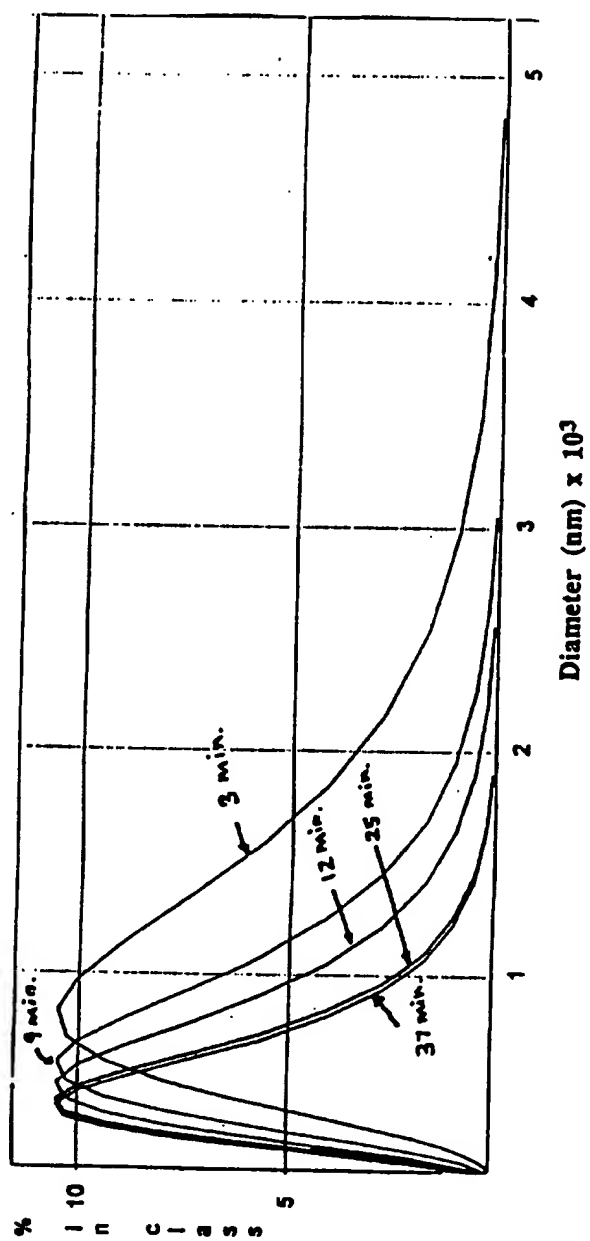


Fig. 6

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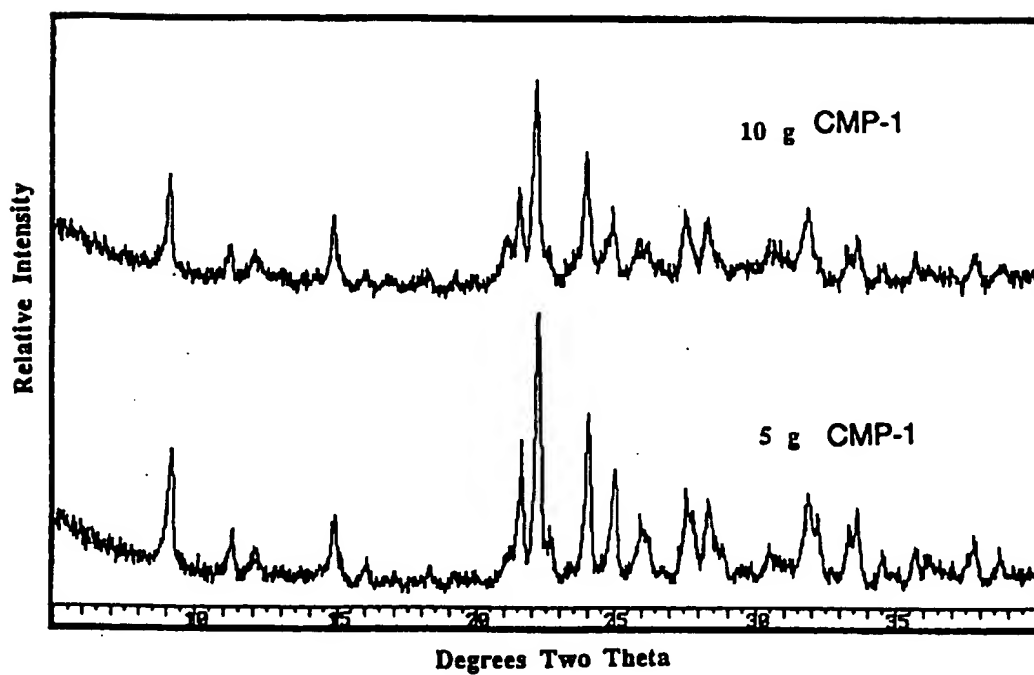


Fig. 7



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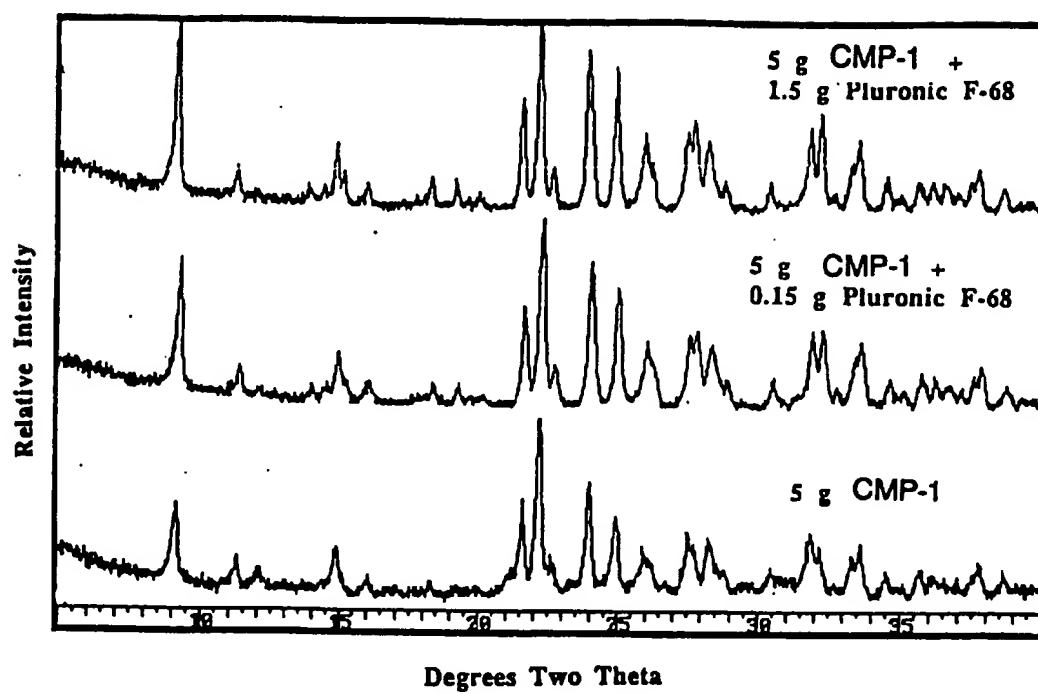


Fig. 8

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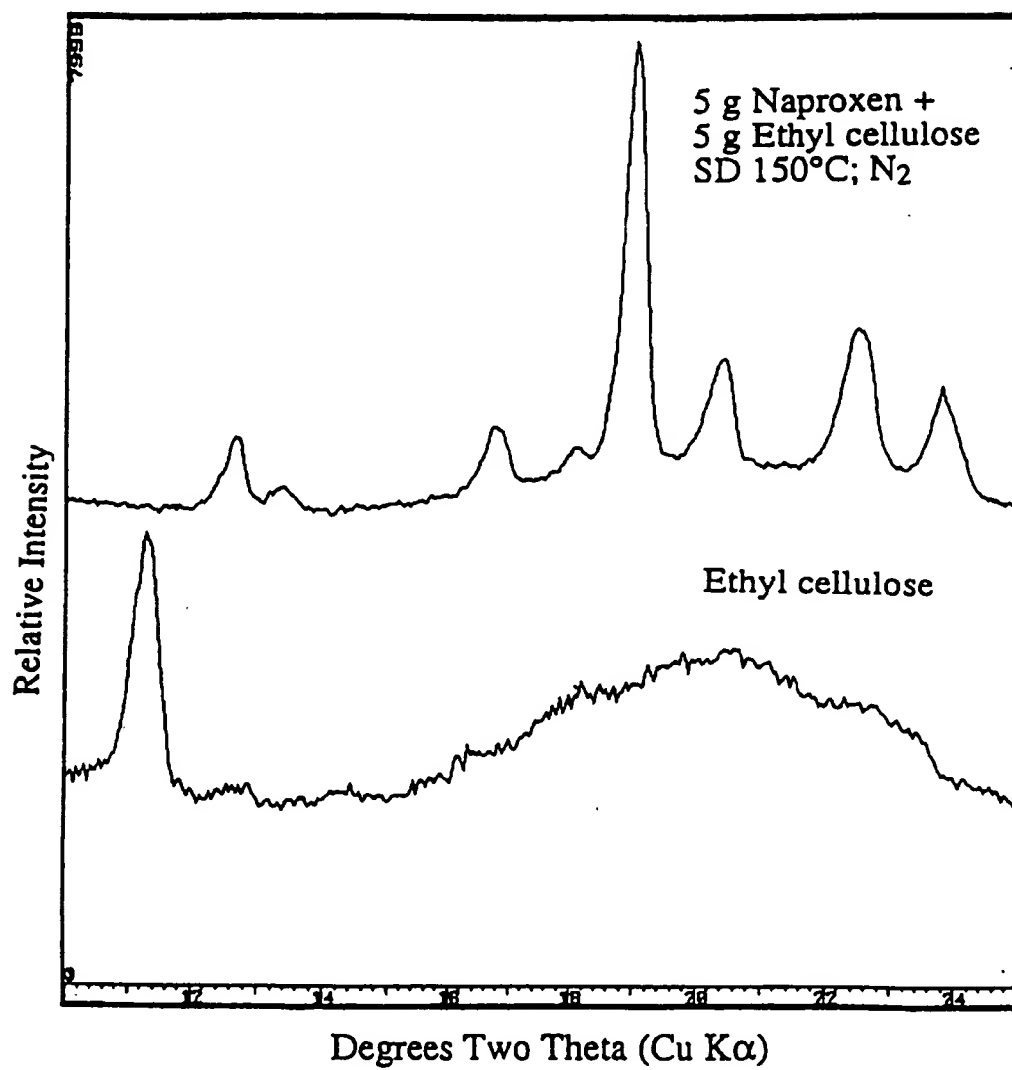


Fig. 9

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/16417

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/16; B29B 9/00, 9/12

US CL : 424/489, 499, 501, 502; 264/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/489, 499, 501, 502; 264/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,107,288 A (OPPENHEIM ET AL.) 15 August 1978, entire document.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
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Date of the actual completion of the international search 30 JANUARY 1997	Date of mailing of the international search report 13 FEB 1997
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